REMARKS

Claims 1-23 are pending in the above-identified application. By the present communication, claims 3 and 4 have been amended. Support for the amendments to the claims can be found in the specification including, for example, on page 14, lines 13-23. A marked up version of the amended claims is provided in Appendix A attached hereto.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-23 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification while being enabling for a method of determining an increased or decreased risk of developing colorectal cancer by determining the relative change in the quantity of nucleic acids between cancerous and noncancerous cells, does not reasonably provide enablement for determining any clinical outcome of a subject with any cancer. In making the rejection, the Office Action relies upon Vogelstein, Trends in Genetics 9:138-141 (1993) in alleging that the art is unpredictable because cancer arises from the accumulation of several mutation in genes for several different growth control circuits and that the identity of the genes is not yet known. The Office Action also alleges that one skilled in the art would be required to perform a study to measure the GDF for patients with many types of cancers to correlate a GDF with a clinical outcome and that although the amount of experimentation is not in and of itself necessarily undue, would be replete with trial and error.

Applicants respectfully traverse the rejection. The specification teaches a method that can be used to determine a clinical outcome of a subject with any cancer. The specification provides exemplary teaching regarding using the methods to determine the clinical outcome of a subject with colorectal cancer. The methods exemplified for colorectal cancer can be applied to any cancer as taught, for example, on page 5, lines 6-11 which teach that "a general method of determining the prognostic clinical outcome of a subject with cancer has been invented."

The specification teaches routine methods for determining a clinical outcome of a subject with any cancer. According to the guidance provided in the specification, those skilled in the art would have known that a clinical outcome determined by the claimed methods is a probability or risk of a cancer-related outcome. In this regard, the specification teaches on page 14, lines 13-23 that determining a clinical outcome refers to determining risk factors. Additionally, the specification teaches on page 20, lines 14-23, that the methods involving measurement of genomic damage can be used to measure survivability which can be determined as a risk for recurrence of the disease.

A Genomic Damage Fraction or GDF can be used in the methods of the invention to predict a clinical outcome. Specifically, the specification teaches on page 13, lines 13-17 that the methods can be used to establish a predetermined GDF "by measuring the GDF for a group of individuals with cancer and

correlating this information with actual clinical outcome for the individuals." The specification teaches routine methods for establishing a predetermined GDF for any cancer including, for example, obtaining genomic DNA from appropriate cancer and normal tissues as taught, for example, on page 32, line 5, through page 33, line 6; determining relative change in quantity of nucleic acids in cancer and normal tissues as taught, for example, on page 15, line 20, through page 16, line 31, and determining a GDF from the results as described, for example, on page 17, lines 1-27. The methods taught in the specification for determining a predetermined GDF for a reference group of individuals with a cancer can also be routinely applied to any individual diagnosed with the cancer. As taught on page 10, lines 13-18, the GDF determined for the individual can be compared to the predetermined GDF to determine the clinical outcome of the individual.

Applicants respectfully submit that any unpredictability for cancer diagnosis allegedly described by Vogelstein is non-analogous to the claimed methods. Specifically, any alleged unpredictability in identifying a particular mutation or combination of mutations involved in a particular cancer is not relevant to the claimed methods because a clinical outcome can be determined in the claimed methods by measuring genomic damage independent of knowledge of the particular sequences that cause the cancer. In this regard, the specification teaches on page 27, lines 17-22, that the methods can be performed independent of sequences information. Moreover, the specification teaches that arbitrarily primed polymerase

chain reaction (AP-PCR) can be used in measuring GDF. As described on page 3, lines 6-23, and as the name implies, primers are chosen arbitrarily for use in AP-PCR, thereby not requiring knowledge of specific sequences that cause a particular cancer.

Further teaching that the methods can be performed independent of knowledge of a particular mutation is provided on page 24, lines 4-9, which teaches that the methods give "an overall picture of the extent of genetic damage in tumor cells." Moreover, because the methods do not require knowledge of a particular mutation associated with a particular cancer and because an overall picture of the extent of genetic damage is provided, the methods can be used to identify previously unidentified genomic regions relevant for cancer diagnosis as described, for example, on page 25, lines 14-33.

Applicant disagrees with the assertion in the Office Action that to practice the invention the skilled artisan would have to perform a study measuring the GDF of patients with many different types of cancers to correlate a GDF with a clinical outcome. The specification teaches that a GDF was correlated to a clinical outcome of colorectal cancer without requiring a determination of GDF for patients with many different types of cancers. According to the teaching and guidance provided in the specification, those skilled in the art would have been able to routinely establish a predetermined GDF correlated with a clinical outcome for individuals having a particular cancer without establishing GDF for other different types of cancer. Applicants submit that trial and error would not have been

required to use the claimed invention because the routine methods taught in the specification, and described above, would have been sufficient to use the claimed methods to determine any clinical outcome of a subject with any cancer. Accordingly, Applicants request that this ground for rejection be removed.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 3 and 4 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In this regard, the Office Action alleges that the claims are indefinite because it is unclear how one would correlate increased risk and decreased risk with a clinical outcome.

Applicants respectfully traverse the rejection and point out that the specification teaches on page 14, lines 13-23, that determining the clinical outcome of a subject with cancer refers to whether the subject will have an increased risk of the recurrence of the cancer including, for example, poor prognosis, such as an increased rate of progress of a cancer and/or increased likelihood the cancer will become metastatic. According to the teaching in the specification, it is sufficiently clear that the recited clinical outcome is increased or decreased risk of the recurrence of the cancer. Nevertheless, in order to further prosecution of this application, Applicants have amended the claims to recite that the clinical outcome is increased or decreased risk of the

recurrence of the cancer. Accordingly, Applicants respectfully request that this ground of rejection be removed.

Rejection under 35 U.S.C. § 102(a)

Claims 1-23 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Arribas et al. J. Clin. Oncol. 15:3230-3240 (1997). In this regard, the Office Action alleges that Arribas et al. describes a method of prognosing colorectal cancer using a genomic damage fraction to compare normal and tumor tissue DNA finger prints.

Applicants respectfully traverse the rejection on the ground that the cited publication is not by another. A Declaration to this effect is currently under review by the inventor and will be subsequently filed in a Supplemental Response to the Office Action. Accordingly, upon review of the Supplemental Response removal of this rejection is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call Cathryn Campbell or the undersigned agent.

Respectfully submitted,

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APPENDIX A

Versions of amended claims 3 and 4 with markings to indicate changes:

3. (Amended) The method of claim 1, wherein said first clinical outcome is increased risk of the recurrence of said cancer.

4. (Amended) The method of claim 1, wherein said second clinical outcome is decreased risk of the recurrence of said cancer.